

Carcinoma of the Ampulla of Vater: Is Radical Lymphadenectomy Beneficial to Patients With Nodal Disease?

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This study was undertaken to evaluate the effectiveness of radical lymphadenectomy in ampullary cancer with nodal disease. Thirty-five patients underwent the Whipple procedure with radical lymphadenectomy. The location and number of positive nodes was characterized. Eighteen patients (51%) had positive nodes. Patients without nodal disease (pN0 group) had an actuarial 5-year survival rate of 81%. Seven patients with metastasis confined to the pancreaticoduodenal nodes had a 5-year survival rate of 67%, which was comparable to the pN0 group (N.S.) and better than the 27% 5-year survival rate in patients with positive superior mesenteric nodes ($P < 0.05$). Eleven patients with one to three positive nodes had a 5-year survival rate of 71%, which was also comparable to the pN0 group (N.S.) and better than the 0% 5-year survival rate in patients with four or more positive nodes ($P < 0.01$). Radical lymphadenectomy is effective against a limited degree of nodal disease. © 1996 Wiley-Liss, Inc.

KEY WORDS: ampulla of Vater neoplasms, ampullary cancer, radical surgery, lymph node excision, prognosis

INTRODUCTION

Carcinoma of the ampulla of Vater (ampullary carcinoma) has better patient survival rates than duct cell carcinoma of the pancreas. Despite the usually poor prognosis of patients with nodal disease [1–8], some have extended survival after pancreaticoduodenectomy [4–9]. A subgroup of patients with nodal disease likely to benefit from radical lymphadenectomy has not been identified. Although some investigators advocate aggressive lymphadenectomy, benefits of radical lymphadenectomy have not been sufficiently proven [8–10].

The aims of this study were to identify factors influencing the survival of those with nodal disease and to evaluate the effectiveness of radical lymphadenectomy.

procedure with radical lymphadenectomy as the treatment of choice for this disease. Eight patients had a bypass procedure because of disseminated disease and were excluded from this study. All other patients underwent a resection. Two patients were excluded: one underwent a pylorus-preserving pancreaticoduodenectomy instead of a classic Whipple procedure by his request, and one underwent the radical Whipple procedure combined with a partial hepatectomy for a metastatic deposit in the liver and died of hepatic recurrence 21 months later. The remaining 35 consecutive patients, who had no evidence of distant metastasis and underwent the classic Whipple procedure with radical lymphadenectomy, were selected as our study subjects. There were 14 women and 21 men

MATERIALS AND METHODS

From 1978 to 1993, 45 patients with histologically proven ampullary carcinoma were referred to our department. During this period we employed a classic Whipple

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whose ages ranged from 45 to 82 (average 60.9 years). No operative deaths within 30 days of an operation or no in-hospital deaths were encountered during this study period.

The classic Whipple procedure used during this period consisted of resection of the distal two-thirds of the stomach to prevent marginal ulceration, division of the pancreas over the portal vein, and division of the bile duct just above the confluence of the cystic duct. Lymph nodes along the choledochus, the portal vein, the hepatic arteries, the gastric wall, and on the right side of the superior mesenteric artery were dissected en bloc together with the nodes attached to the resected pancreas. Total pancreatectomy was not performed in this series. A partial resection of the portal vein was done in a patient with invasion.

Pathologic findings were documented using the TNM (tumor, nodes, metastases) system [11]. The names of lymph node groups around the head of the pancreas have not been standardized internationally [8,11–15]. In this study, the pancreaticoduodenal nodes were defined as those located either along the posterior and anterior pancreaticoduodenal arteries (=arterial arcades) or on the surface of the head of the pancreas according to Rouvière and Tobias [12], Evans and Ochsner [13], Cubilla et al. [14], and the Japanese Society of Biliary Surgery [15]. This group of lymph nodes is the most important of the first echelon node groups of the periampullary region [8,12,14,15]. The superior mesenteric nodes were defined as those located around the superior mesenteric artery [8,12,13,15].

Lymph nodes were identified in resected specimens and dissected out. Particular lymph node groups, especially the superior mesenteric node group, had been labeled at surgery in order to help identify them in the en bloc specimens. The number of dissected lymph nodes per case ranged from 13 to 73 (mean 37.4, median 32). They were examined histologically to detect metastatic foci on a single representative section per lymph node. The TNM system [11] considers metastasis to regional lymph nodes as a group (N1). In this study, we arbitrarily subdivided N1 into two subsets: N1a, metastasis confined to the pancreaticoduodenal nodes; and N1b, metastasis involving the superior mesenteric nodes (without regard to nodal metastasis to the other sites). pN1, pN1a, and pN1b denote pathologic N1, N1a, and N1b, respectively.

Clinical records and follow-up data were obtained for all 35 patients. Actuarial survival rates were calculated by the Kaplan–Meier method. Differences in survival curves were measured using the generalized Wilcoxon test. A difference was regarded as statistically significant at $P \leq 0.05$.

RESULTS

Nodal disease was found in 18 patients (51%). The number of positive nodes ranged from 1 to 24 (mean 4.3,

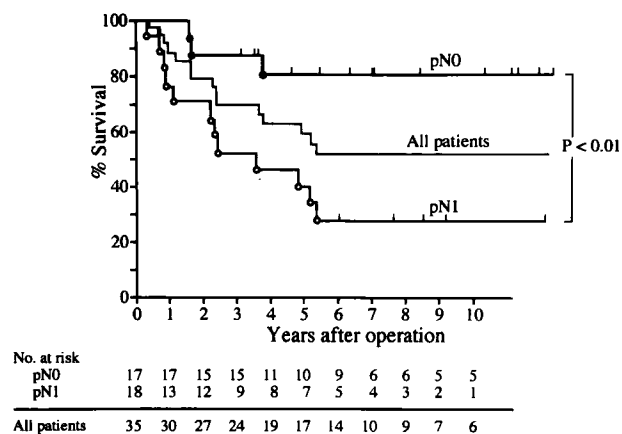


Fig. 1. Survival curves of all patients, patients with nodal disease (pN1), and patients without nodal disease (pN0). The 5-year survival rates were 60%, 41%, and 81%, respectively. Statistical significance: pN0 vs. pN1, $P < 0.01$.

median 2.5). The 5-year survival rates of patients without nodal disease (pN0) and those with nodal disease (pN1) were 81% and 41%, respectively (Fig. 1). A significant survival difference ($P < 0.01$) was seen between patients with and without nodal disease. Metastasis was not identified in any of the perigastric lymph nodes and nodes along the hepatic artery.

Location of Positive Nodes

Patients were divided into three subsets: pN0 (17 patients); pN1a (seven patients); and pN1b (11 patients). The 5-year survival rates of pN0, pN1a, and pN1b groups were 81%, 67%, and 27%, respectively (Fig. 2). The survival curve of the pN1a group was significantly better than that of the pN1b group ($P < 0.05$), and comparable to that of the pN0 group (N.S.).

Number of Positive Nodes

Patients were divided into three subsets according to the number of positive nodes: 0 positive nodes (pN0, 17 patients); 1–3 positive nodes (11 patients); and ≥ 4 positive nodes (seven patients). The 5-year survival rates of the pN0, “1–3 positive nodes” and “ ≥ 4 positive nodes” groups were 81%, 71%, and 0%, respectively (Fig. 3). The survival curve of the “1–3 positive nodes” group was significantly better than that of the “ ≥ 4 positive nodes” group ($P < 0.01$) and comparable to that of the pN0 group (N.S.).

Five-Year Survivors With Lymph Node Metastasis

Clinicopathologic findings in the seven patients who had nodal disease and survived 5 years after resection are listed in Table I. Two patients died of recurrence beyond 5 years after resection. All the survivors showed fewer than four positive nodes. A potentially curative (RO) resection was done in all.

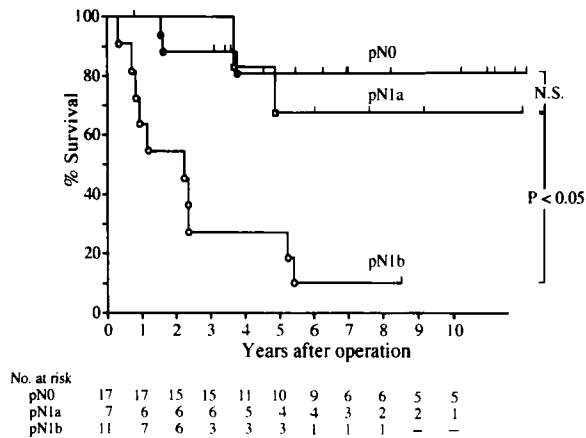


Fig. 2. Survival curves according to the location of positive nodes. No nodal disease is denoted as pN0. Metastasis confined to the pancreaticoduodenal nodes and metastasis to the superior mesenteric nodes were arbitrarily designated as pN1a and pN1b, respectively. The 5-year survival rates were 81%, 67%, and 27%, respectively. Statistical significance: pN0 vs. pN1a, N.S.; pN1a vs. pN1b, $P < 0.05$; pN0 vs. pN1b, $P < 0.001$.

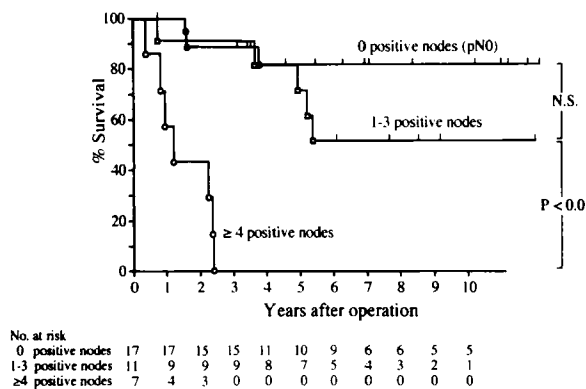


Fig. 3. Survival curves according to the number of positive nodes. The 5-year survival rates for 0, 1-3 and ≥ 4 positive nodes were 81%, 71%, and 0%, respectively. Statistical significance: "0-positive nodes" vs. "1-3 positive nodes," N.S.; "1-3 positive nodes" vs. " ≥ 4 positive nodes," $P < 0.01$; "0-positive nodes" vs. " ≥ 4 positive nodes," $P < 0.001$.

DISCUSSION

This study indicates that the location and number of positive nodes are significant prognostic factors. The survival rate of patients with either fewer than four positive nodes or metastasis confined to the pancreaticoduodenal group was comparable to that of patients without nodal disease. These results indicate that radical lymphadenectomy is effective against a limited degree of nodal disease. Many investigators have reported nodal disease as an important prognostic factor [1-8]. However, the impact of the location and number of positive nodes on survival

has not been fully described. Fortner [9], Henne-Bruns et al. [10], and Mori et al. [8] have performed pancreaticoduodenectomy with aggressive radical lymphadenectomy for periampullary tumors with a mortality rate ranging from 6.2% to 17% but have failed to clearly prove the effectiveness of such a radical procedure.

Three patients with pN1b disease survived more than 5 years (5-year survival rate of 27%). Mori et al. [8] have also reported a patient with pN1b disease surviving 5 years after a radical pancreaticoduodenectomy. Thus, we think that a radical pancreaticoduodenectomy should not be contraindicated for patients with metastasis involving the superior mesenteric nodes when a potentially curative resection is feasible. Two patients with pN1b disease died more than 5 years after resection. Such late recurrences have been reported [2,3,6,16]. As all recurrences occurred within 6 years in our series, follow-up evaluation is mandatory for at least this period.

Limitations

This study has the following limitations: an uncontrolled study, the small number of patients, and the short-term follow-up in some cases. However, this study could present more 5-year survivors with nodal disease than previous reports. While our results seem to favor the use of node dissections, without a randomized controlled study, it is also possible that the results are partly due to a heterogeneity of intrinsic biological aggressiveness among node positive ampullary tumors; i.e., some of those tumors may not be biologically aggressive.

It is sometimes impossible to differentiate ampullary cancer from other periampullary tumors pre- or intraoperatively. However, we recommend a radical approach in these doubtful cases, because they include ampullary and duodenal cancers with better prognosis following radical surgery.

Another limitation is some variability occurred in the extent and degree of the dissection of the superior mesenteric nodes according to the individual surgeon's preference. It is likely that a standardized radical nodal dissection would have resulted in improved outcomes. Further investigations using carefully defined radical nodal dissection by the same surgeon may be necessary to decide the value of lymphadenectomy.

Clinical Implications

This study has several clinical implications. First, the effectiveness of radical lymphadenectomy may justify an aggressive approach to ampullary cancer with nodal disease. Second, surgery alone may be sufficient when nodal disease is absent or limited on histologic examination. Adjuvant therapy may be indicated for patients with severe nodal disease, although the effectiveness

TABLE I. Ampullary Carcinoma With Lymph Node Metastasis—Five-Year Survivors After Whipple Procedure and Radical Lymphadenectomy

Patient	Age (yr)/sex	pT ^a	pN ^a	M ^a	Stage ^a	Residual tumor (R) ^a	Positive nodes		Outcome (mo)
							Location	N	
1	55/F	2	1	0	III	0	PD	1	142; NED
2	45/M	2	1	0	III	0	PD	3	110; DOO (suicide)
3	75/F	3	1	0	III	0	PD, SM	2	101; NED
4	80/F	1	1	0	III	0	PD	1	91; NED
5	63/M	2	1	0	III	0	PD	1	72; NED
6	67/M	2	1	0	III	0	SM	1	64; DOD (HEP)
7	60/F	2	1	0	III	0	PD, SM	2	61; DOD (HEP)

^aRefer to the TNM system [11] for details.

PD, pancreaticoduodenal nodes; SM, superior mesenteric nodes; NED, alive with no evidence of disease, DOO, died of other causes; DOD, died of disease; HEP, hepatic recurrence.

of adjuvant treatment has not been proven [17]. Third, 51% of our patients had nodal disease. The previously reported rates of nodal disease have been lower, ranging from 21% to 47% [3,5–8,17,18]. This discrepancy can be explained by the detailed examination of dissected regional lymph nodes performed in this study. The high rate of nodal metastasis may explain why local resection often shows recurrence even with negative margins [3,19]. Many authors have advocated pylorus-preserving pancreaticoduodenectomy for periampullary tumors [4,20,21]. The fact that nodal disease was not found in perigastric nodes in this study provides further support for the pylorus-preserving procedure. Considering the high rate of nodal disease in advanced stages [21], we believe that radical lymphadenectomy is mandatory when performing a pylorus-preserving procedure for most cases of ampullary cancer, excluding cases of “early cancer” [21].

CONCLUSIONS

Metastasis confined to the pancreaticoduodenal nodes and a small number of positive nodes are favorable prognostic factors in patients with nodal disease. Radical lymphadenectomy seems to be effective against a limited degree of nodal disease, and should not be contraindicated for all patients with nodal disease when a potentially curative resection is feasible.

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